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Supplemental Data**

Fragile X and X-Linked Intellectual Disability:

Four Decades of Discovery

Herbert A. Lubs, Roger E. Stevenson, and Charles E. Schwartz

Table S1. Genes Involved in X-Linked Intellectual Disability (by Year of Discovery)

Year	Gene Name	Gene Symbol	XLID Entity (OMIM Numbers)	Function	How Found	REF
1983	Hypoxanthine guanine phosphoribosyl transferase	<i>HPRT</i>	Lesch-Nyhan 308000	Enzyme	Met-Fu	1
1983	Phosphoglycerokinase 1	<i>PGK1</i>	Phosphoglycerokinase deficiency 311800	Enzyme	Met-Fu	2
1985	Proteolipid protein	<i>PLP</i>	PMP, SPG1 300401	Myelination	Mol-Fu	3
1986	Ornithine transcarbamoylase	<i>OTC</i>	Ornithine transcarbamoylase deficiency 300461	Enzyme	Met-Fu	4
1987	Dystrophin	<i>DMD</i>	Duchenne muscular dystrophy 300377	Structure of skeletal muscle membrane	Chr-rea	5
1989	Pyruvate dehydrogenase	<i>PDHA1</i>	Pyruvate dehydrogenase deficiency 312170	Enzyme	Met-Fu	6
1990	Iduronate sulfatase	<i>IDS</i>	Hunter 309900	Lysosomal enzyme	Met-Fu	7
1991	Fragile X intellectual disability 1	<i>FMR1</i>	Fragile X 300624	RNA-binding protein, gene regulation	Chr-rea L-can	8
1992	Cell adhesion molecule, L1	<i>L1CAM</i>	XLHS, MASA, ACC, X-linked; SPG2 308840	Neuronal migration, cell adhesion	L-can	9
1992	Norrie	<i>NDP</i>	Norrie 310600	Neuroectodermal cell interaction	Chr-rea	10
1992	Oculorenal	<i>OCRL1</i>	Lowe 309000	Enzyme	Chr-rea	11
1993	Adrenoleukodystrophy protein	<i>ABCD1 (ALDP)</i>	Adrenoleukodystrophy 300371	Peroxisomal transport protein	L-can	12
1993	Copper transporting ATPase 7A	<i>ATP7A</i>	Menkes, occipital horn 300011	Copper transport	Chr-rea	13
1993	Monoamine oxidase A	<i>MAOA</i>	Monoamine oxidase A deficiency 309850	Enzyme	L-can	14
1995	X-linked nuclear protein, X-linked helicase 2	<i>ATRX (XNP, XH2)</i>	Alpha-thalassemia intellectual disability, Carpenter-Waziri, Chudley-Lowry, Holmes-Gang, Juberg-Marsidi, XLID-hypotonic facies, XLID-spastic paraplegia, XLID-arch fingerprints-hypotonia, MRX 300032	Transcription factor, helicase activities	L-can	15
1996	Dystonia-deafness peptide	<i>TIMM8A (DDP)</i>	Mohr-Tranebjaerg, Jensen 300356	Transcription factor	L-can	16

1996	Faciogenital dysplasia	<i>FGD1</i> (<i>FGDY</i>)	Aarskog-Scott, MRX 305400	Guanine nucleotide exchange factor	Chr-rea	17
1996	Fragile X intellectual disability 2	<i>AFF2</i> (<i>FMR2</i>)	Fragile XE 309548	Unknown	Chr-rea	18
1996	Glycerol kinase deficiency	<i>GKD</i>	Glycerol kinase deficiency 300474	Metabolism, glycerol uptake	Met-Fu	19
1996	Glypican 3	<i>GPC3</i>	Simpson-Golabi-Behmel 300037	Cell adhesion, motility	L-can	20
1996	Myotubularin	<i>MTM1</i>	Myotubular myopathy 300415	Tyrosine phosphatase	L-can	21
1997	Midline 1	<i>MID1</i>	Telecanthus/Hypo- spadias, Opitz G/BBB 300000	Zinc finger gene	L-can, Chr-rea	22
1997	Rab GDP-dissociation inhibitor 1	<i>GDI1</i>	MRX41, 48 300104	Stabilizes GDP bound conformations	L-can	23
1997	Threonine-serine kinase 2	<i>RPS6KA3</i> (<i>RSK2</i>)	Coffin-Lowry, MRX19 300075	Kinase signaling pathway	L-can	24
1998	Doublecortin	<i>DCX</i>	Lissencephaly, X-linked 300121	Neuronal migration	Chr-rea (del)	25
1998	Dyskerin	<i>DKC1</i>	Dyskeratosis congenita 300126	Cell cycle and nucleolar functions	L-can	26
1998	Filamin 1	<i>FLNA</i> (<i>FLN1</i>)	Periventricular heterotopias, OPDI, OPDII 300017	Actin-binding protein	L-can	27
1998	Oligophrenin 1	<i>OPHN1</i>	XLID-cerebellar dysgenesis, MRX60 300127	GTPase activating protein	L-can	28
1998	P21-activated kinase	<i>PAK3</i>	MRX30, 47 300142	Rac/Cdc 42 effector	Chr-rea	29
1999	IL-1 receptor accessory protein-like	<i>IL1RAPL</i>	MRX21, 34 300206	Unknown	Chr-rea	30
2000	Lysosomal associated membrane protein 2	<i>LAMP2</i>	Danon cardiomyopathy 309060	Membrane, lysosome	L-can	31
2000	NF- κ B essential modulator	<i>IKB6KG</i> (<i>NEMO</i>)	Incontinentia pigmenti 300248	Activates the trans- cription factor NF- κ B	L-can	32
2000	Rho guanine nucleotide exchange factor 6	<i>ARHGEF6</i> (α - <i>PIX</i>)	MRX46 300267	Effector of the rho GTPases	Chr-rea	33
2000	Transmembrane 4 superfamily member 2	<i>TSPAN7</i> (<i>TM4SF2</i>)	MRX58 300096	Interacts with integrins	Chr-rea	34
2001	Creatine transporter	<i>SLC6A8</i>	Creatine transporter deficiency, MRX 300036	Creatine transporter	Met-Fu	35
2001	Methyl-CpG binding protein 2	<i>MECP2</i>	Rett, MRX16, 64, 79 3000005	Binds methylated CpGs	L-can	36
2001	Oral-facial-digital syndrome I	<i>OFD1</i>	Oral-facial-digital I 300170	Unknown	L-can	37
2002	Angiotensin-II receptor type 2	<i>AGTR2</i>	Optic atrophy, X-linked; MRX88 300034	Angiotensin II receptor	Chr-rea	38

2002	Aristaless-related X chromosome gene	<i>ARX</i>	Hydranencephaly, Partington, Proud, West, lissencephaly with abnormal genitalia, X-linked; MRX29, 32, 33, 36, 43, 54, 76 300382	Neuronal migration	Chr-rea (del)	39
2002	Fatty acid acyl CoA synthetase type 4	<i>ACSL4 (FACL4)</i>	MRX63, 68 300157	Fatty acid CoA ligase 4	Chr-rea (del)	40
2002	Kruppel-like factor 8	<i>KLF8 (ZNF741)</i>	MRX 300286		Chr-rea	41
2002	PHD-like zinc finger gene 6	<i>PHF6</i>	Börjeson-Forsman-Lehmann 300414	Unknown	L-can	42
2002	Serine-threonine kinase 9	<i>CDKL5 (STK9)</i>	Rett-like seizures-hypotonia; MRX 300203	Unknown	Chr-rea	43
2002	SRY-box 3	<i>SOX3</i>	XLID-growth hormone deficiency 313430	Pituitary function, transcription factor	Chr-rea L-can	44
2003	Immunoglobulin-binding protein 1	<i>IGBP1</i>	Graham coloboma 300139		L-can	45
2003	Nance-Horan syndrome gene	<i>NHS</i>	Nance-Horan 300457		L-can	46
2003	Neurologin 3	<i>NLGN3</i>	Autism, MRX 300336	Cell adhesion	L-can	47
2003	Neurologin 4	<i>NLGN4</i>	Autism, MRX 300427	Cell adhesion	L-can	48
2003	Polyglutamine tract binding protein 1	<i>PQBP1</i>	Renpenning, Sutherland-Haan, Hamel cerebro-palatocardiac, Golabi-Ito-Hall, Porteous, MRX55 300463	Polyglutamine binding, regulates transcription	L-can	49
2003	Spermine synthase	<i>SMS</i>	Snyder-Robinson 300105	Synthesis of spermine	L-can	50
2003	Zinc finger 41	<i>ZNF41</i>	MRX89 314995	Zinger finger	Chr-rea	51
2003	Zinc finger 81	<i>ZNF81</i>	MRX45 314998	Zinc finger	Chr-rea	52
2004	BCL6 corepressor	<i>BCOR</i>	Lenz microphthalmia (1 type) 300485	Histone/protein deacetylation	L-can	53
2004	Jumonji, AT-rich interactive domain 1C	<i>KDM5C (SMX, JARID1C)</i>	MRX 314690	Regulates transcription, chromatin remodeling	L-can	54
2004	K1AA1202 protein	<i>SHROOM4 (KIAA1202)</i>	Stoccos dos Santos 300579	Roles in cellular architecture, neurulation, and ion channel function	Chr-rea	55
2004	KIAA2022 protein	<i>KIAA2022</i>	Cantagrel spastic paraplegia	DNA synthesis, DNA polymerase activity	Chr-rea	56

			300524			
2004	Methyl transferase	<i>FTSJ1</i>	MRX9, 44 300499	Methylase	L-can	57
2004	Neuroendocrine DLG	<i>DLG3</i>	MRX8, 90 300189	NMDA-receptor, mediated signaling, synaptic plasticity	X seq	58
2004	PFD finger protein 8	<i>PHF8</i>	XLID-cleft lip-cleft palate 300560	Regulates transcrip- tion, binds DNA	L-can	59
2004	Renin receptor	<i>ATP6AP2</i> (<i>ATP6A8-9</i>)	XLID-infantile epilepsy 300556	Renin receptor	L-can	60
2004	Rho guanine nucleotide exchange factor 9	<i>ARHGEF9</i>	XLID-hypotonia-seizures 300429	Regulation of Rho protein signal transduction	Chr-rea	61
2004	Synapsin 1	<i>SYN1</i>	Epilepsy-macrocephaly 313440	Synaptic vesicle protein	L-can	62
2004	T3 transporter	<i>SLC16A2</i> (<i>MCT8</i>)	Allan-Herndon-Dudley, MRX 300095	T3 receptor	L-can	63
2005	Zinc finger DHHC domain-containing protein 15	<i>ZDHHC15</i>	MRX91 300576		Chr-rea	64
2006	Fanconi anemia complementation group B protein	<i>FANCB</i>	VACTERL-hydrocephaly 300515	DNA repair	Mol-Fu	65
2006	Holocytochrome C synthase	<i>HCCS</i>	MIDAS syndrome 300056	Energy production, cytochrome homolyase	Chr-rea (del)	66
2006	Sigma 2 subunit of adaptor protein/complex	<i>AP1S2</i>	Turner, XLID- hydrocephaly-basal ganglia calcification, MRX59 300629	Assembly of endocytic vesicles	X-seq	67
2006	SMC1 structural maintenance of chromosomes 1-like	<i>SMC1L1</i> (<i>SMC1A</i>)	Cornelia de Lange syndrome, X-linked 300040	Cell cycle, mitotic spindle organization and biogenesis, chromosome segregation	Mol-Fu	68
2006	Sushi repeat containing protein, X-linked	<i>SRPX2</i>	XLID-Rolandic seizures, MRX 300642	Signal transduction, growth factor 2	Mol-Fu	69
2006	Ubiquitin-conjugating enzyme E2A	<i>UBE2A</i>	XLID-nail dystrophy- seizures 312180	Ubiquitin cycle, ubiquitin-protein ligase	L-can	70
2006	Zinc finger protein 674	<i>ZNF674</i>	XLID-retinal dystrophy- short stature, MRX92 300573	Transcription regulation	Chr-rea (del)	71
2007	Bromodomain and WD repeat domain-containing protein 3	<i>BRWD3</i>	XLID-macrocephaly- large ears, MRX93 300553	Transcription factor	X-seq	72
2007	Cullin 4B	<i>CUL4B</i>	XLID-hypogonadism- tremor 300304	Cell cycle, ubiquitin cycle, E3 ubiquitin ligase	X-seq	73

2007	Drosophila porcupine homolog	<i>PORCN</i>	Goltz 300651	Wnt receptor signaling pathway, acyltransferase activity, integral to membrane of endoplasmic reticulum	Chr-rea (del)	74
2007	Glutamate receptor ionotropic AMPA 3	<i>GRIA3</i>	Chiyonobu XLID, MRX94 305915	Signal transduction, ion transport, glutamate signaling pathway	Chr-rea Exp-Arr X-seq	75
2007	Hydroxyacyl-coenzyme A dehydrogenase, type III	<i>HADH2 (HSD17B10)</i>	XLID-choreoathetosis 300256	Lipid metabolism	L-can	76
2007	Mediator of RNA polymerase II transcription, subunit 12	<i>MED12 (HOPA)</i>	Opitz FG, Lujan 300188	Transcription regulation, RNA polymerase II transcription mediator activity, ligand-dependent nuclear receptor transcription coactivator activity, vitamin D receptor and thyroid hormone receptor binding	L-can	77
2007	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex	<i>NDUFA1</i>	Mitochondrial complex 1 deficiency, MRX 300078	Energy production, oxidoreductase activity	Mol-Fu	78
2007	Nuclear RNA export factor 5	<i>NXF5</i>	XLID-short stature-muscle wasting 300319	mRNA processing, mRNA export from nucleus	Chr-rea	79
2007	Phosphoribosyl pyrophosphate synthetase 1	<i>PRPS1</i>	Arts, PRPS1 superactivity 311850	Ribonucleotide monophosphate biosynthesis	L-can	80
2007	Ribosomal protein L10	<i>RPL10</i>	Autism 312173	Protein synthesis, ribosomal protein	X-seq	81
2007	UPF3 regulator of nonsense transcript homolog B	<i>UPF3B</i>	MRX62, Lujan/FG phenotype 300298	mRNA catabolism, nonsense mediated decay	X-seq	82
2007	Zinc finger, DHHC-domain containing protein 9	<i>ZDHHC9</i>	XLID-macrocephaly-Marfanoid habitus 300646	?	X-seq	83
2008	E3 ubiquitin-protein ligase	<i>HUWE1</i>	MRX17, 31; Juberg-Marsidi 300697	Ubiquitin-protein ligase, mRNA transport	M-CGH X-seq	84
2008	Protocadherin 19	<i>PCDH19</i>	Epilepsy and intellectual disability limited to females 300460		L-can	85
2008	Magnesium transporter 1	<i>MAGT1 (IAP)</i>	MRX95	Magnesium transporter with an N-glycosylation sites and putative phosphorylation sites	L-can X-seq	86

2008	Sodium-hydrogen exchanger NHE6	<i>SLC9A6</i>	Christianson, X-linked Angelman-like syndrome 300231	Sodium-hydrogen antiporter activity, lysosome organization and biogenesis, regulation of endosome volume	L-can X-seq	87
2008	Calcium/calmodulin-dependent serine protein kinase	<i>CASK</i>	Intellectual disability and microcephaly with pontine and cerebellar hypoplasia (MICPCH); Intellectual disability and nystagmus	Signal transduction, protein trafficking, synaptic function	Chr-rea X-seq L-can	88
2009	Intramembrane zinc metalloprotease	<i>MBTPS2</i>	Ichthyosis follicularis, atrichia, photophobia syndrome 300294	Protease activity, activates signaling proteins	L-can X-seq	89
2009	NAD(P)H steroid dehydrogenase-like	<i>NSDHL</i>	CK (microcephaly, pachygyria, facial dysmorphism, seizures) 300275	Sterol metabolism	L-can X-seq	90
2010	Small GTPase gene	<i>RAB39B</i>	MRX72 and a syndrome with macrocephaly, seizures, and autism 300774	Formation and maintenance of synapse	L-can	91
2010	Guanine nucleotide exchange factor	<i>IQSEC2</i>	MRX1, MRX18 and other nonsyndromal XLID 300522	Regulation of vesicular transport and organelle structure	X-seq	92
2010	Patched domain-containing 1	<i>PTCHD1</i>	Autism-XLID, MRX	Transmembrane protein related to hedgehog receptors	M-CGH	93
2011	RAS-associated protein RAB40A-like	<i>RAB40AL</i>	Martin-Probst 300519	Ras-like GTPase protein located in mitochondria	Chr-rea L-can X-seq	94
2011	RNA-binding motif protein	<i>RBM10</i>	TARP (311900)	RNA-binding	X-seq	95
2011	N-acetyltransferase subunit 10	<i>NAA10</i>	N-alpha-acetyltransferase deficiency (300013)	N-terminal acetylation	X-seq	96
2011	Las1-like protein	<i>LAS1L</i>	Wilson-Turner (309585)	Nucleolar protein cell proliferation and ribosome biogenesis	X-seq	97
2011	Eukaryotic translation initiation factor 2	<i>EIF2S3</i>	MEHMO (300148)	Initiates translation	X-seq	98
2011	Host cell factor C1	<i>HCFC1</i>	MRX3	Cell proliferation	X-seq	99
2011	THO complex, subunit 2	<i>THOC2</i>	MRX12	mRNA transcription or export	X-seq	100
2011	Chloride channel voltage-gated 4	<i>CLCN4</i>	MRX49	Chloride transport	X-seq	100
2011	Histone deacetylase 8	<i>HDAC8</i>	Cornelia de Lange, X-linked (300590)	Chromatin cohesion	Mol-Fu	101

Chr-rea = chromosome rearrangement

Exp-Arr = expression array
L-can = linkage and candidate gene testing
M-CGH = array-comparative genomic hybridization
Met-Fu = exploitation of metabolic alteration
Mol-Fu = exploitation of molecular finding
X-seq = brute force sequencing

Table S2. XLID Syndromes that Have Not Been Mapped

Syndrome	Phenotype	REF
Agenesis of the Corpus Callosum, X-linked	Developmental retardation, small head size, enlarged ventricles, hypoplasia of the inferior vermis and cerebellum, right ptosis, adducted thumbs, upper limb weakness, and Hirschsprung disease.	102
Ataxia-Deafness-Dementia, X-linked [301790]	Optic atrophy, deafness, hypotonia, progressive ataxia, and seizures.	103
Ataxia-Spastic Diplegia	Short stature, muscle hypoplasia, nystagmus, ataxia and spastic.	104
Atkin-Flaitz (300431)	Short stature, macrocephaly, coarse facial features, broad short hands with tapered fingers, macroorchidism, and seizures.	105
Bergia Cardiomyopathy	Myopia, slowly progressive scapuloperoneal muscular dystrophy and hypertrophic cardiomyopathy.	106
Branchial Arch, X-linked	Microcephaly, branchial arch defects, hearing loss, and cryptorchidism.	107
Cantu [308830]	Short stature, microcephaly, alopecia, and seizures.	108
Cerebral-Cerebellar-Coloboma	Hydrocephaly, cerebellar vermis hypoplasia, agenesis of corpus callosum, retinal colobomas, hypertelorism, small nose, micrognathia, areflexia, seizures, hypotonia, childhood death.	109
Cerebro-Oculo-Genital	Microcephaly, short stature, microphthalmia, agenesis of the corpus callosum, hypospadias or other genital anomalies, and spastic quadriplegia.	110
Clark-Baraitser [300602]	Macrocephaly, prominent forehead and large ears, broad nasal tip, thick lower lip, prominent supraorbital ridges, small lateral maxillary incisors, obesity, and macroorchidism.	111
Craniofacioskeletal [300712]	Females with mild ID, microcephaly, short stature, facial distinctiveness, small hands and feet and excessive fingerprint arches. Males died in infancy with craniofacial, cardiac and genital abnormalities.	112
Fitzsimmons ¹¹³	Lower limb spasticity, pes cavus, and hyperkeratosis of the palms and soles.	113
Giuffré-Tsukahara [603438]	Microcephaly, variable facial findings, radioulnar synostosis.	114
Hall Orofacial	Cleft lip and palate, hypertelorism, inguinal hernia.	115
Homfray Seizures-Constrictions	Coarse facies, progressive joint constrictions and seizures.	116
Hyde-Forster [300064]	Brachycephaly, flat occiput, plagiocephaly, coarse facial features, and severe developmental delay.	117
Hydrocephaly-Cerebellar Agenesis [307010] ¹¹⁸	Hydrocephaly, cerebellar agenesis, hypotonia, seizures, and early death.	118
Hydrocephaly-Microphthalmia-Chondroplasia	Hydrocephaly, microcephaly, short nose, undermineralization of skull, spondylometaphyseal dysplasia.	119
Kang	Microcephaly, frontal prominence, telecanthus, down-turned mouth, short broad hands with brachydactyly, agenesis of	120

	corpus callosum, and spastic diplegia.	
Microcephaly-Testicular Failure	Microcephaly, short stature and hypogonadism.	121
Optic Atrophy, X-linked [311050]	Optic atrophy, ataxia tremors, absent ankle deep tendon reflexes, and emotional liability.	122
Paine [311400]	Microcephaly, optic atrophy, spastic diplegia, and seizures.	123
Pallister W	Short stature, characteristic facies (high forehead, frontal upsweep, prominent brow, hypertelorism, downslanting palpebral fissures, depressed and broad nasal bridge, wide nasal tip, incomplete cleft lip and palate, short high mandible).	124
Pettigrew [304340]	Long narrow face, microcephaly or hydrocephaly, Dandy-Walker malformation, seizures, spasticity, choreoathetosis, and iron deposition in the basal ganglia.	125
Plott ¹²⁶	Laryngeal abductor palsy.	126
Roifman [300258]	Short stature, retinal dystrophy, immunodeficiency, spondyloepiphyseal dysplasia.	127
Say-Meyer [314320]	Short stature, microcephaly, hypotelorism, and craniosynostosis.	128
Schimke [312840]	Short stature, microcephaly, strabismus, sunken eyes, thin nose, impaired vision and hearing, abducens palsy, choreoathetosis, and spasticity.	129
Smith-Fineman-Myers	Microdolichocephaly, upslanting palpebral fissures, ptosis, strabismus, cupped ears, flat philtrum, maxillary overbite, thin upper lip, scoliosis, bridged palmer creases, and long narrow feet with midfoot varus.	130
Stoll	Short stature, prominent forehead, broad nasal tip with anteverted nares, hypertelorism, and hypotonia.	131
Urban	Short stature, small hands and feet with digital contractures, osteoporosis, obesity, and genital anomalies.	132
Vasquez	Short stature, microcephaly, hypotonia, obesity, hypogonadism, and gynecomastia.	133
Warkany	Intrauterine growth retardation, short stature, and microcephaly, ptosis, cupped ears, thin neck, and flat chest.	134
Wittwer [300421]	Growth failure, microcephaly with large fontanelles, frontal prominence, hypertelorism, long philtrum, thin upper lip, cupped ears, blindness, hearing loss, and seizures.	135
XLID Ataxia-Dementia [301840]	Progressive ataxia, pyramidal signs, and adult-onset dementia.	136
XLID-Ataxia-Apraxia	Ataxia and dyspraxia with variable cognitive function.	137
XLID-Hypospadias	Normal stature, microcephaly, trigonocephaly, synophrys, midface hypoplasia, beaked nose, posteriorly rotated ears with folded helices and arched palate.	138
XLID-Psoriasis [309480]	Hypertelorism, large ears, macrostomia with arched upper lip, prominent lips, hypotonia, childhood-onset psoriasis, and seizures.	139
XLID-Retinitis Pigmentosa	Microcephaly and retinitis pigmentosa.	140
XLID-Spastic Paraplegia-Athetosis [312890]	Spastic paraplegia, weakness, dysarthria, and nystagmus.	141
XLID-Spondyloepimetaphyseal Dysplasia	Short stature, distinctive facies, spondyloepimetaphyseal dysplasia.	142
XLID-Thyroid Aplasia-Cutis	Short stature, cutis gyrata over the vertex of the scalp, signs of	143

Verticus Gyrata	myxedema, diastasis rectus, ulnar deviation of the hands, and severe intellectual disability with aphasia.	
XLID with Thyroxine-Binding Globulin Deficiency [314200]	Thyroxine-binding globulin deficiency.	144
Young-Hughes	Short stature, obesity, hypergonadotropic hypogonadism, chronic dermatitis, strabismus, and seizures.	145

Supplemental References

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